Scientific Abstract

The objective of this study is to investigate the safety of non-virally transfected autologous human fibroblasts producing human factor VIII (hFVIII) when implanted within the peritoneum of patients with severe hemophilia A. Nine (9) patients with severe hemophilia A who have a history of effective treatment with factor VIII replacement therapy will be included in the study.

Following informed consent and study enrollment, a sample of skin will be obtained by punch biopsy and transferred promptly to the pilot manufacturing facility of Transkaryotic Therapies Inc. (TKT). Dermal fibroblasts will be isolated from the skin biopsy and expanded in culture. The fibroblasts will be transfected by electroporation with a plasmid encoding hFVIII. Stably transfected fibroblasts expressing hFVIII will be selected and cloned, and one fibroblast clone will be expanded for implantation into the patient. The production of an autologous clone of fibroblasts expressing hFVIII will require approximately seven weeks.

Each patient will be implanted with a specified number of hFVIII-expressing fibroblasts derived from a single autologous clone. The autologous fibroblasts will be implanted in the peritoneum using a laparoscopic procedure. The patients will be hospitalized overnight following the implantation and will receive factor VIII replacement therapy prior to and for six days following the implantation procedure.

This is a dose escalation study, beginning with 100×10^6 transfected autologous fibroblasts and sequentially escalating to 200×10^6 and 400×10^6 transfected fibroblasts. Three patients will be included in each dose level. The patients will be evaluated during a 12 week intensive follow up period using physical examination, adverse events, routine clinical laboratory tests, specialized hematology laboratory tests, and patient diaries (evaluating bleeding episodes and factor VIII usage). Subsequent to the intensive 12 week follow up period, patients will enter into the long-term phase of the study, where they will be followed for an additional 21 months.